Unfavorable Structural and Functional Outcomes in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis

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Abstract: BACKGROUND Recurrent optic neuritis (rON) associated with myelin oligodendrocyte glycoprotein (MOG)-specific antibodies has been initially reported to show a better clinical outcome than aquaporin-4 (AQP4)-seropositive ON in neuromyelitis optica spectrum disorder (NMOSD). Here, we characterize clinical and neuroimaging findings in severe cases of MOG antibody-positive and AQP4 antibody-negative bilateral rON. METHODS Three male adults with rON (ages 18, 44, and 63 years) were evaluated with optical coherence tomography (OCT), MRI, cerebrospinal fluid (CSF), and serological studies. RESULTS All patients experienced >7 relapses of ON with severe reduction of visual acuity and partial response to steroid treatment. Optic nerves were affected bilaterally, although unilateral relapses were more frequent than simultaneous bilateral recurrences. Patients were MOG-seropositive but repeatedly tested negative for AQP4 antibodies. OCT showed severe thinning of the peripapillary retinal nerve fiber layer. On MRI, contrast-enhancing lesions extended over more than half the length of the optic nerve. CSF analyses during ON episodes were normal. Severe visual deficits accumulated over time in 2 of 3 patients, despite immunosuppressive therapy. CONCLUSIONS MOG-seropositive and AQP4-seronegative rON may be associated with an aggressive disease course and poor functional and structural outcomes. In contrast to previous reports, the severity and pattern of retinal and optic nerve damage closely resembled phenotypes commonly observed in AQP4-seropositive rON without fulfilling current diagnostic criteria for NMOSD.

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Methods: Three male adults with rON (ages 18, 44, and 63 years) were evaluated with optical coherence tomography (OCT), MRI, cerebrospinal fluid (CSF), and serological studies.

Results: All patients experienced >7 relapses of ON with severe reduction of visual acuity and partial response to steroid treatment. Optic nerves were affected bilaterally, although unilateral relapses were more frequent than simultaneous bilateral recurrences. Patients were MOG-seropositive but repeatedly tested negative for AQP4 antibodies. OCT showed severe thinning of the peripapillary retinal nerve fiber layer. On MRI, contrast-enhancing lesions extended over more than half the length of the optic nerve. CSF analyses during ON episodes were normal. Severe visual deficits accumulated over time in 2 of 3 patients, despite immunosuppressive therapy.

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Myelin oligodendrocyte glycoprotein (MOG)-specific antibodies have been detected in peripheral blood of pediatric patients with acute disseminated encephalomyelitis (ADEM), but also in adults with benign, unilateral cerebral cortical encephalitis, aquaporin-4 (AQP4)-seronegative neuromyelitis optica spectrum disorder (NMOSD), AQP4-seronegative brainstem encephalitis, AQP4-seronegative (often longitudinally extensive) transverse myelitis, or in subjects with AQP4-seronegative optic neuritis (ON) (1–7). Because classic NMOSD is considered an astrocytopathy, and MOG antibody–associated diseases primarily display demyelination in the central nervous system, it has been a matter of debate whether MOG-seropositive, AQP4-seronegative syndromes should be classified as NMOSD, or whether they rather represent a separate autoimmune disease entity (8,9). MOG-seropositivity has been reported to be more frequently associated with simultaneous bilateral ON,

a monophasic disease course and a better functional outcome as compared to AQP4-seropositivity (10–14). Only recently have severe MOG antibody–associated recurrent ON (rON) been described (5,9,15,16). We evaluated 3 adult male patients with severe MOG antibody–positive rON and our aggressive immunosuppressive treatment attempts that could not prevent significant structural and/or functional sequelae.

METHODS

Patients provided written informed consent according to Swiss legislation; the use of clinical data was approved by the Cantonal Ethical Committee of Zurich, Switzerland (EC-ZH-No. 2013-0001). All patients received MRI and cerebrospinal fluid (CSF) examinations as routine diagnostic workup. Mean peripapillary retinal nerve fiber layer (pRNFL) thickness and macular volumes were assessed by optical coherence tomography (OCT) using a Spectralis SD-OCT device (Heidelberg Engineering, Heidelberg, Germany). Visual acuity (VA) was measured using Snellen charts; high- and low-contrast VA were assessed using ETDRS-style and 2.5% contrast SLOAN charts, respectively. Serum anti-MOG and anti-AQP4 antibodies were measured at the Clinical Department of Neurology, Innsbruck Medical University, by a cell-based assay as previously described (3). All patients were diagnosed with MOG-associated rON after excluding other diagnoses.

CASE REPORTS

Patient 1

A 18-year-old man experienced ON with subacute, painful visual loss in his right eye to hand movements. After high-dose corticosteroid, acuity in the right eye improved to 20/200. One month after the onset of ON, he experienced focal motor sensory and secondary generalized seizures. CSF analysis revealed normal cell count and protein levels without oligoclonal bands (OCBs). Brain MRI showed contrast enhancement over half the lengths of both optic nerves and the optic chiasm, as well as multiple T2- and contrast-enhancing lesions in the corpus callosum. Epileptic seizures subsided when the patient was treated with levetiracetam. Over the next 4 months, he experienced an episode of chiasmitis and 3 episodes of left ON. Treatments included high-dose corticosteroids and plasma exchange on 5 occasions.

Six months after his initial episodes of visual loss, he was referred to our institution. VA was 20/125, right eye, and worse than 20/400, left eye. pRNFL thickness was reduced in both eyes (right 46 μm and left 84 μm), with preferential thinning of the papillomacular bundle and the nasal and temporal quadrants (see **Supplemental Digital Content 2**, Fig. E1, http://links.lww.com/WNO/A308). Sera obtained on 3 occasions over a span of 10 months revealed MOG antibodies with titers ranging from 1:160 to 1:640. AQP4-antibody tests were repeatedly negative. MOG antibody–associated chronic relapsing inflammatory optic neuropathy (CRION) was diagnosed.

Over the 6 months after our initial evaluation, the patient experienced 1 episode of right ON and 2 of left ON, despite continuous treatment with oral steroids (5–100 mg/day), use of rituximab 2×375 mg/m^2, and plasma exchange. Notably, these episodes occurred during tapering the dose of steroids, and each responded moderately to high-dose oral steroids (100 mg/day over 5 days). Nine months after his initial episode, MRI showed persistent contrast enhancement of both optic nerves.

During the next 7 months, mycophenolate mofetil (up to 3,000 mg/day) was added as additional therapy. MRI no longer showed optic nerve enhancement. After repeating rituximab (1×375 mg/m^2), disease activity stabilized. At last follow-up, VA was 20/200, right eye, and no light perception, left eye, with pRNFL thickness of 28 μm in each eye.

In summary, 5 of 9 ON events were not only severe, but led to severe residual visual deficits. Rituximab therapy reduced relapse frequency, but could not prevent legal blindness (acuity worse than 20/200) as final outcome. The addition of mycophenolate mofetil to rituximab ameliorated the visual deficit on the right eye over time (see **Supplemental Digital Content 1**, Table E1, http://links.lww.com/WNO/A307).

Patient 2

A 43-year-old man was referred with an 8-year history of severe, painful rON. He initially experienced right ON with MRI showing edema and contrast enhancement along the entire right optic nerve. CSF analysis was normal. Subsequently, he had 1 additional episode of right ON, 4 of left ON, and 1 episode occurred bilaterally resulting in legal blindness. Although VA during ON episodes was reduced to as low as finger counting on both sides, the patient initially responded well to high-dose corticosteroid treatment. Therapy with azathioprine over 6 months was unsuccessful in preventing ON relapses. Repeat MRIs over 5 years showed exclusive optic nerve enhancement, whereas the spinal cord seemed normal. Multiple CSF analyses were normal. A diagnosis of CRION was made.

On our examination, VA was 20/20, right eye, and 20/32, left eye. OCT revealed pRNFL thinning (right: 48 μm; left: 52 μm) (See **Supplemental Digital Content 2**, Fig. E1, http://links.lww.com/WNO/A308). The patient ultimately stabilized, after rituximab (375 mg/m^2) was given (See **Supplemental Digital Content 1**, Table E1, http://links.lww.com/WNO/A307). Most recently, acuity was 20/16 in both eyes. On 2 occasions, serum tested positive for MOG antibodies (titers 1:1,280 and 1:2,560) and negative for AQP4 antibodies.

Generally, Patient 2 recovered well after each of 10 ON events including severely disabling events. Rituximab

treatment reduced relapse frequency and may have stabilized the disease course in this patient.

Patient 3

A 59-year-old man experienced subacute back pain, urinary retention, saccadic smooth pursuit, and fever 6 weeks after an influenza vaccination. CSF analysis revealed an elevated cell count (183/μL) without OCB. MRI showed multiple T2-hyperintense bilateral thalamic, mesencephalic, pontine, and cervical, thoracic and lumbar spinal lesions with contrast enhancement of the thalamic, mesencephalic, pontine, and thoracic lesions. Microbiology and virology testing was negative, as was screening for AQP4 antibodies. A diagnosis of ADEM was made.

Two months later, he experienced painful right ON, with VA of 20/40. MRI demonstrated edema and contrast enhancement of almost the entire length of the right optic nerve. He was treated with high-dose corticosteroids, yet suffered a relapse of painful right ON. One month later, natalizumab (300 mg monthly) was added to the treatment regimen, but 3 further relapses of painful right ON occurred within 2 months. With a combination of intravenous high-dose steroids and plasma exchange, VA recovered to 20/40 in the right eye. Two months later, he received rituximab (375 mg/m^2), and 1 month later, another 1000 mg.

Nevertheless, 2 months after the last rituximab infusion, he developed painful left ON and was given monthly infusions of cyclophosphamide (600–1100 mg/m^2/cycle) for 13 months. During that time, the patient had 2 additional episodes of right ON. Repeat CSF analysis was unremarkable. Monthly infusions of tocilizumab (8 mg/kg) led to 17 months without relapse. VA was light perception, right eye, and 20/25, left eye. Measurement of pRNFL thickness was 30 μm, right eye, with thinning over all quadrants (See **Supplemental Digital Content 2**, Fig E1, http://links.lww.com/WNO/A308), and 62 μm, left eye, with predominant thinning over the nasal and inferior quadrants. MRI demonstrated atrophy of the right optic nerve and multiple supratentorial, T2-hyperintense lesions, but resolution of all spinal cord lesions. MOG antibodies were detected at a titer of 1:160 on 2 occasions but negative for AQP4 antibodies.

In summary, 4 of 8 ON events were severe and led to disabling residual visual deficits. Rituximab and cyclophosphamide treatment, respectively, reduced relapse frequency, but could not prevent severe ON relapses. Only initiation of tocilizumab therapy stabilized the disease completely without any further relapses or visual deterioration (See **Supplemental Digital Content 1**, Table E1, http://links.lww.com/WNO/A307).

DISCUSSION

We present 3 adult male patients with MOG antibody–associated rON (MOG-ON) with poor structural outcomes in all cases and poor functional outcomes in 2 of 3 cases. None of our patients fulfilled current diagnostic criteria for NMOSD (17). Two patients experienced an ADEM-like episode after (Patient 1) or before (Patient 3) their first episode of ON. In accordance with previous reports (16,18), CSF findings were normal in 2 patients during MOG-ON episodes. The initial elevated CSF cell count and mild blood–brain barrier dysfunction in Patient 3 may be related to the antecedent influenza vaccination and suggestive of both MOG-seropositive ADEM and NMOSD, as both have been reported to feature increased CSF cell counts (12,19). To the best of our knowledge, this is only the third case with vaccination-related MOG-seropositive disease (9). Other MOG-seropositive cases have been associated with viral or bacterial infection including influenza virus infection, Epstein–Barr virus-induced infectious mononucleosis and *Chlamydia pneumoniae* infection (20–22). In these cases, autoreactive MOG antibody–producing B cells may be activated by both the simultaneous uptake of the cognate autoantigen (MOG) and the "bystander" viral antigen (e.g., influenza hemagglutinin) into B cells from infected parenchymal cells and by T cells specific for the respective antigen (23).

Extensive contrast enhancement of the optic nerve (frequently extending over more than half of the entire length and involving the chiasm) on MRI and marked thinning of the entire pRNFL resembled typical findings in NMOSD (24). OCT studies have shown preferential temporal pRNFL thinning in multiple sclerosis–associated rON, whereas the initial involvement of the superior and inferior quadrants is typical in NMOSD-associated rON along with severe macular thinning (24,25). By contrast, in all 3 patients with MOG-ON reported here, pRNFL thickness was reduced in all quadrants.

Tapering of corticosteroid therapy led to ON relapses in Patient 1. Dependency on long-term corticosteroid treatment and good responsiveness to high-dose corticosteroid treatment are typical of CRION. MOG-seropositive CRION and rON cases with rapid steroid response and increased relapse risk after steroid cessation have been reported (4,9,16). Notably, Patients 1 and 2 showed only partial clinical response to antibody-targeted therapy with rituximab.

Within the past few years, the first MOG-ON cases with the onset of >18 years of age have been reported (15,16). These patients tended to show worse VA outcome than pediatric cases (15). However, only 2 of 14 patients in these reports (Case 10 (15); Case 7 (16)) experienced such a severe reduction of VA like the cases presented here. Subsequently, other cases with recurrent (14,27) and/or severe disease course have been described (9,28,29). As reports of MOG-seropositive patients with longer follow-up (>5 years) become available, poor visual outcomes will likely become more prevalent.

Because MOG-ON reportedly affects female patients more often than male patients, with higher annualized relapse rate in female patients (9), the cases reported here (all men and frequent rON) may represent one end of the spectrum of MOG-ON. Whether the later onset of MOG-ON and/or gender of the individual is associated with a more aggressive disease course warrants further study. Testing for MOG antibodies should be considered in cases of rON or suspected NMOSD, particularly in patients with AQP4-seronegative. Notably, MOG antibody titers did not relate to ON severity or pRNFL loss. Future studies including larger case series will have to address the pathological relevance and overall clinical utility of MOG-antibody testing for clinical decision making.

In summary, our cases suggest that MOG-ON may be associated with disabling structural and functional visual outcomes, similar to patients with AQP4-seropositive ON. Initiation of high efficacy immune therapy should be evaluated early in these patients, especially when initial episodes are followed by poor visual outcome.

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